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## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference  SCH-1703 WO	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.  PCT/US00/20064	International filing date (day/month/year)  24/07/2000	Priority date (day/month/year)  22/07/1999
International Patent Classification (IPC) or national classification and IPC  C07D417/06		
Applicant  SCHERING AKTIENGESELLSCHAFT et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input checked="" type="checkbox"/> Certain documents cited</li> <li>VII <input checked="" type="checkbox"/> Certain defects in the international application</li> <li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand  14/02/2001	Date of completion of this report  28.09.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Fazzi, R  Telephone No. +49 89 2399 8510



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**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-42                    as originally filed

**Claims, No.:**

1-7                    as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description,                pages:
- the claims,                    Nos.:
- the drawings,                sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.
- claims Nos. 1-4.

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-4 are so unclear that no meaningful opinion could be formed (*specify*):  
see separate sheet
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)                    Yes: Claims 5-6  
                                  No: Claims 7

Inventive step (IS)           Yes: Claims 5-6  
                                 No: Claims 7

Industrial applicability (IA)   Yes: Claims 5-7

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No: Claims

2. Citations and explanations  
see separate sheet

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)  
and / or

2. Non-written disclosures (Rule 70.9)  
see separate sheet

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
see separate sheet

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
see separate sheet

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**1) Reference is made to the following documents:**

D1: NICOLAU K.C. ET AL: 'Total syntheses of epothilones A and B via a macro-lactonization-based strategy' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 34, 27 August 1997 (1997-08-27), pages 7974-7991, XP002156412 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 cited in the application

D2: WO 97 19086 A, cited in the application

**1.1) Intermediate documents (Reference to section VI)**

In view of D3 having a publication date of 04/02/2000, the priority of the current application has been checked and has been found valid for the whole subject-matter claimed. Thus, the content of D3 is not considered to be comprised in the state of the art and will not be used in the present International Preliminary Examination Report.

D3: MARTIN H.J. ET AL.: 'How stable are epoxides? A novel synthesis of epothilone B' ANGEWANDTE CHEMIE. INTERNATIONAL EDITION., vol. 39, no. 3, 4 February 2000 (2000-02-04), pages 581-583, XP002156413 VERLAG CHEMIE. WEINHEIM., DE ISSN: 0570-0833

**2) The present application relates to a process for the production of epothilone B and derivatives thereof as well as intermediate products for this process (cf. claims 5-6). It also relates to general compounds disclosed in claim 7.**

**3) Non-establishment of opinion and clarity (Reference to sections III and VIII)**

Claims 1-4 are so broad and unclear that no meaningful opinion could be formed. In fact they lack all the **technical features** which are necessary for the definition of the invention, because it is not sufficient to disclose only the intermediates of the reaction, but it is also necessary to state **how** the reaction is carried out. For example, in claim 1 it is mentioned that the method comprises the cyclization of an **undefined** compound from an intermediate of formula II, but nothing is said about the process involved. Also in claim 4, **no technical feature** is disclosed which would allow the reader to clearly understand the scope of the invention.

Moreover it is not clear which extension is covered by the expression "epothilone compounds"; from the description it seems it comprises only epothilone A and B, but other derivatives can be ascribed to this expression which might not be within the scope of the application. Therefore, claim 1 does not clearly identify the final products to be achieved. Thus, the examination will be based only on those claims in which the reagents, the intermediates and the final products, together with the reaction conditions are clearly defined.

Furthermore it is suggested that dependent claims precisely describing the course of the several reactions should be incorporated in the corresponding independent claims.

**Remarks:** in claim 1, the group R<sup>4</sup> is not defined.

**4) Novelty (Reference to section V)**

*4.1) Product claim 7*

The subject-matter of claim 7 does not meet the requirements of Article 33(2) PCT as formulas 16 and 21 have already been disclosed in, respectively, D1 and D2 (cf. compound 19 on page 7975, scheme 2, right-hand column of D1 and formula 7, on page 3 and 31 of D2).

*4.2) Process claims 5-6*

With respect to D1 and D2, the subject-matter of claims 5 and 6 meets the criteria of Article 33(2) PCT as the reaction steps they describe have not been specifically disclosed in the cited documents.

**5) Inventive step (Reference to section V)**

The problem to be solved by the present application may be regarded as how to provide an alternative method for the production of epothilone "compounds", where, in particular, the cis-epoxide is introduced at a considerably earlier time if compared with the processes currently in use.

Document D1, which is considered to represent the most relevant state of the art, discloses (cf. pages 7977-7979) a total synthesis of epothilone B, from which the subject-

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matter of claims 5-6 differs in that the cis-epoxide is introduced at a considerably earlier time via dihydroxylation-monosulfonation of a (E)-olefin (cf. page 3, lines 7-12 of this application).

In view of documents D1 and D2 (D2 appears not to be relevant), the solution proposed in claims 5-6 of the present application is non-obvious because the provision of the epoxy compound 11 represents a surprising effect over the state of the art. In fact, in all previous synthesis the epoxidation reaction was always carried out in the last step, as the resulting epoxide was expected to be labile. In the present case, the Applicant has shown by means of example that compound 11 is stable under different reaction conditions (cf. page 4 and 5) and that, therefore, a new synthesis of epothiolone B can be made, which represents a teaching, namely a contribution over what has been disclosed up to now in the field of methods for the production of natural substances with antitumor properties such as epothiolone B.

Accordingly, the subject-matter of claims 5-6 meets the requirements of Article 33(3) PCT.

**6) Further observations (Reference to section VII)**

**6.1)** According to the requirements of Rule 10.2 PCT, the terminology and the signs shall be consistent throughout the application. This requirement is not met because, in claim 1, formula II should actually read formula 11, as this is the numbering which can be found in the description on page 6 and in claims 5 and 7. It is recommended to always adopt the same reference sign when referring to a particular formula.

**6.2)** In claim 7 it is not explained what "Bn" and "PMB" mean when referring to the R group.

**6.3)** On page 11, the sentence starting with "the following preferred.." and ending with "..in any way whatsoever" and on page 42, lines 5-9 should be amended as they imply that the extent of protection may be expanded in some vague and not precisely defined way (cf. PCT Guidelines, section IV, III-4.3a).

**6.4)** Some pages of the description (cf. for example page 3 and 11) and the diagrams are hardly legible. The Applicant is therefore asked to file new corrected pages.

**6.5)** In claim 7, in figures where the groups RO and POG are present, the carbon atoms

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should be bound to the oxygen atoms and not to the R or PG groups, like erroneously typed in formulas 5-8.